

Remarks

Claims 1-27, 32, 36, 37, 69 and 77 are pending. Claims 28-31, 39, and 70-74 stand withdrawn. Reconsideration is requested in view of the above changes and the following remarks.

The specification is amended to correct an inadvertent clerical error. Scheme 15 inadvertently did not appear in the published International specification. The content of Scheme 15 is described in the preceding paragraph in the specification at p. 71, lines 20-22, which makes reference to the inadvertently omitted scheme.

Claim Amendments

Claim 1 is re-written to include the limitations of canceled claim 4, with the following changes. The substituent option “-(C₁-C₈)hydrocarbyl” has been deleted from the revised term “R^b attached to aryl” while the revised term “R^b attached to heteroaryl” retains all substituents that were originally in claim 4.

Claim 2 is amended to comport with the changes to claim 1, from which it depends. Since the scope of Formula I has been narrowed to a compound of Formula IA, it would be evident to a skilled artisan from the teachings of the disclosure that the compound of Formula IA_z as claimed also includes all of the limitations of the compound of claim 1, the one further limitation being definition of the Z-configuration of the carbon-carbon double bond. Support can be found in the specification at p. 23, lines 20-24; and at p. 35, lines 23-25 which describes embodiments of compound IA as claimed.

Claim 3 is amended to comport with the changes to claim 1, from which it depends. Since the scope of Formula I has been narrowed to a compound of Formula IA, it would be evident to a skilled artisan from the teachings of the disclosure that the compound of Formula IA_e as claimed also includes all of the limitations of the compound of claim 1, the one further limitation being definition of the E-configuration of the carbon-carbon double bond. Support can be found in the specification at p. 23, lines 15-20; and at p. 26, line 31 to p. 27, line 27, also at p. 36, lines 13-26 which describes embodiments of compound IA as claimed.

Claim 4 is canceled.

Claim 5 is amended to depend from claim 1.

Claim 10 is amended to depend from claim 8 in order to correct a clerical error, and thus establish proper antecedent basis for the compounds claimed in claim 14.

Claim 11, which depends from claim 10, is amended to comport with the changes to claim 1, from which it ultimately depends. In this claim, the substituent option “(C₁-C₆)alkyl” is deleted from the term R^b.

Claim 14 is amended to comport with the changes to claim 1, by the deletion of four species compounds.

Claim 15, which depends from claim 10, is amended to comport with the changes to claim 1, from which it ultimately depends. In this claim, the substituent option “methyl” is deleted from the term R^b.

Claim 18, which depends from claim 10, is amended to comport with the changes to claim 1, from which it ultimately depends. In this claim, the substituent option “(C₁-C₆)alkyl” is deleted from the term R^b. Claim 18 is further amended merely to delete the inadvertent inclusion of the phrase “or a salt thereof,” since only neutral compounds are claimed.

Claim 19 is amended merely to delete the inadvertent inclusion of the phrase “or a salt thereof,” since only neutral compounds are claimed.

Claim 20 is amended to comport with the changes to claim 1, by the deletion of four species compounds.

Claim 23 is amended merely to correct a typographical error, in that the term “thienyl-1-dioxide” is corrected to read “thienyl-1,1-dioxide.” It would be clearly evident to one of ordinary skill in the art that the designation “dioxide” would require two oxygen atoms to be attached to sulfur at the 1-position.

Claims 28, 32, 36 and 37 are amended to depend from claim 10.

Claims 69 and 72 are re-written in independent format.

Response to 103 Rejection

In the Office action of April 2, 2008, claims 1-3 were rejected under 35 U.S.C. 103(a) as unpatentable over Schwan et al., J. Org. Chem, **1998**, 63(22) 7825-2832 ("Schwan et al."). This rejection is maintained in the current Office action.

While Applicants do not agree that the compounds of Schwan et al. render the claims obvious, and although the Examiner has not indicated any specific reason or specific chemical modification of the prior art that would render the claims obvious, in an effort to advance prosecution, Applicants have amended the compound claims to delete the optional substituent "-(C₁-C₈)hydrocarbyl" from the term R^b when ring B¹ is aryl. The group "-(C₁-C₈)hydrocarbyl" (specification, p. 18, lines 7-9) encompasses "(C₁-C₆)alkyl," which includes "methyl" (specification, p. 13, line 30 to p. 14, line 5). Thus, claim 1 has been re-written to include the limitations of former claim 4, except that amended claim 1 does not include "-(C₁-C₈)hydrocarbyl" in the term R^b when ring B¹ is aryl. Consequently, neither does amended claim 1 cover compounds having a methyl substituent on ring B (now B¹) of general Formula I (now IA) when ring B¹ is aryl. The remaining compound claims have been amended consistent with the changes in amended claim 1.

Since the methyl (*i.e.* alkyl or hydrocarbyl) group has been deleted from ring B¹ when the ring is aryl, the claims cannot be rendered obvious over Schwan et al., and the rejection should be withdrawn.

Response to 112, First paragraph Rejection

Claims 32, 36 and 37 have been newly rejected under 35 U.S.C. 112, first paragraph as not enabling for "treating breast tumor, prostate tumor, lung tumor, colorectal tumor and therapeutic ionizing radiation with all of the compounds of general formula I" as claimed, p. 3 of Office action.

As discussed above, Applicants have amended claim 1 to exclude the optional substituent "-(C₁-C₈)hydrocarbyl" from the term R^b when ring B¹ is aryl. The group "-(C₁-

C₈)hydrocarbyl” (specification, p. 18, lines 7-9) encompasses “(C₁-C₆)alkyl,” which includes “methyl” (specification, p. 13, line 30 to p. 14, line 5). Furthermore, Claim 10, in which both the A-ring and the B-ring are defined as phenyl, provides a narrowed genus which is fully supported by the biological data disclosed in the instant specification, as discussed below. Thus the claimed genus as claimed in amended method claims 32, 36 and 37 has been narrowed substantially to the compounds according to claim 10 of general Formula IC.

Amended claims 32, 36 and 37 are fully enabled for treating breast, prostate, lung, and colorectal cancers with the claimed genus of general Formula IC, as follows. Applicants’ specification discloses complete synthetic routes (*e.g.* Schemes 5-8, 11 and 19, with accompanying description in the specification at pp. 55-59, 61 and 87) in conjunction with working examples (*cf.* Examples 29-33 at pp. 87-90) and additional examples (Examples 15-28, Table 5 at pp. 85-86), that would enable a skilled artisan to make and use the claimed compounds of general Formula IC for treating breast, prostate, lung, and colorectal cancers over the full scope of the claims. The Examiner has not shown any reason why a skilled artisan would not be able to make compounds within the full scope of the present claims, without undue burden, and with the expectation of having anticancer activity as determined for representative compounds in Table 7 at p. 92 in the specification. The exemplary compounds of Table 7 possess antitumor activity, and represent no fewer than 4 compound subclasses, *e.g.* **3-nitrobenzyl**, **3-aminobenzyl**, **3-hydroxybenzyl**, and **4-methoxybenzyl** derivatives.

On page 6 of the Office action, the Examiner alleges that “Applicants have not provided any guidance for using the claimed method for treating “breast tumor, prostate tumor, lung tumor, colorectal tumor and therapeutic ionizing radiation with all the compounds of general formula I”,”. Applicants respectfully disagree as follows. The specification at p. 46, line 4 to p. 49, line 18, and p. 78, line 11 to p. 79, line 17, discloses exemplary methods for the treatment of proliferative disorders, particularly cancer, and also radioprotective treatment using therapeutic ionizing radiation, while Example 35 provides experimental data for growth inhibition of 4 tumor cells lines, as claimed. The provided data clearly demonstrates the ability of the claimed compounds to arrest the growth of cancer cells and would be a sufficient teaching

to a skilled person to correlate the use of the claimed compounds in the treatment of cancer as claimed. MPEP 2164.02: *CORRELATION: IN VITRO/IN VIVO*.

On page 7 of the Office action, the Examiner alleges: "In lieu of the fact that no animal models exist which can reasonably suggest successful treating "breast tumor, prostate tumor, lung tumor, colorectal tumor and therapeutic ionizing radiation with all the compounds of general formula I", it will be necessary for an ordinary skilled artisan to have clinical data in order to practice the claimed invention." (underlining added). Applicants do not agree that either animal models or human clinical data are required to establish enablement of the instant claims. Efficacy in a cell model or animal model constitutes a "working example" if that example "correlates" with a disclosed or claimed method invention. Contrary to the Examiner's assertion, as discussed above, a skilled practitioner would reasonably correlate the experimental data in the instant specification to the claimed methods of treatment. MPEP 2164.02: *CORRELATION: IN VITRO/IN VIVO*. See *In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) (reversing the PTO decision based on finding that *in vitro* data did not support *in vivo* applications). Only a reasonable correlation is required – not a rigorous or an invariable exact correlation. See *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985).

In summary, the Examiner has not established a *prima facie* case of lack of enablement, since based on the amendment of the claimed genus to the compounds of Formula IC, and the experimental evidence provided in the instant specification, taken as a whole, a skilled person would not be required to perform undue experimentation to make and use the claimed invention. MPEP 2164.02: *WORKING EXAMPLES AND A CLAIMED GENUS*.

Response to Double Patenting Rejection

Claims 1-27, 32, 36-37, 69 and 77 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as unpatentable over claims 1-6, 8, 94-95, 97-117, 122, 128 and 130-132 of co-pending U.S. Application No. 10/592,604. Without acquiescing in the rejection, applicant notes that the rejection is provisional, since the allegedly conflicting claims in the '604 application have not been patented.

For the convenience of the Examiner, the following is the status of the '604 application. In the '604 application, a Restriction Requirement was issued on March 5, 2008. On April 2, 2008, Applicants elected Group 1, with traverse. In the Office Action mailed June 9, 2008, the Examiner vacated the Election/Restriction in favor of a new restriction/Lack of Unity. In a telephone conversation with Applicants' representative on June 4, 2008, Applicants provisionally elected Group 1 with traverse. On December 9, 2008, Applicants filed an amendment and response to the Office Action, and affirmed election of Group 1. Since the instant application is the earlier-filed application, no response is required at this time. MPEP 1490.V.D.

Request for Rejoinder of Claims 28-31, 39 and 70-71

Claims 28-31 and 39 are directed to conjugates of compounds of claim 10 (claims 28-30), pharmaceutical compositions thereof (claim 31) and methods of treating breast, prostate, lung and colorectal cancer by administration of those conjugates (claim 39). These claims are directed to non-elected inventions that depend from or otherwise require all the limitations of an allowable claim to an elected invention, namely claim 10.

Accordingly, rejoinder and allowance of claims 28-31 is requested pursuant to MPEP 821.04(a):

Rejoinder Between Product Inventions; Rejoinder Between Process Inventions.

When restriction was required between independent or distinct products, or between independent and distinct processes, and all claims directed to an elected invention are allowable, any restriction requirement between the elected invention and any nonelected invention that depends from or otherwise requires all the limitations of an allowable claim should be withdrawn."

For the same reason, rejoinder and allowance of claim 39 is requested pursuant to MPEP 821.04(b):

Rejoinder of Process Requiring an Allowable Product.

Where claims directed to a product and to a process of making and/or using the product are presented in the same application, applicant may be called upon under 35 U.S.C. 121 to elect claims to either the product or a process. See MPEP § 806.05(f) and § 806.05(h). The claims to

the nonelected invention will be withdrawn from further consideration under 37 CFR 1.142. See MPEP § 821 through § 821.03. However, if applicant elects a claim(s) directed to a product which is subsequently found allowable, withdrawn process claims which depend from or otherwise require all the limitations of an allowable product claim will be considered for rejoinder. All claims directed to a nonelected process invention must depend from or otherwise require all the limitations of an allowable product claim for that process invention to be rejoined. Upon rejoinder of claims directed to a previously nonelected process invention, the restriction requirement between the elected product and rejoined process(es) will be withdrawn.

Claims 70 and 71 depend from claim 69. The only basis for rejection of claim 69 has been overcome, as discussed above. Claim 69 is therefore allowable. Rejoinder an allowance of claims 70 and 71 is requested, since claims 70 and 71 depend from claim 69. The basis of rejoinder is MPEP 821.04(a), reproduced above.

Conclusion

Applicants respectfully submit that the application is in good and proper form for allowance, and the Examiner is respectfully requested to pass this application to issue. If, in the opinion of the Examiner, another telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,

E. PREMKUMAR REDDY, *et al.*

BY 

DANIEL A. MONACO
Registration No. 30,480
Drinker Biddle & Reath LLP
One Logan Square
18th and Cherry Streets
Philadelphia, PA 19103-6996
Tel: (215) 988-3312
Fax: (215) 988-2757
Attorney for Applicants